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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/780,600 | 02/09/2001 | Joc Y.L. Lam | 4446D1 | 9004 |

22896 7590 08/25/2003

MILA KASAN, PATENT DEPT.
APPLIED BIOSYSTEMS
850 LINCOLN CENTRE DRIVE
FOSTER CITY, CA 94404

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| EXAMINER |
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BAKER, MAURIE GARCIA

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| ART UNIT | PAPER NUMBER |
|----------|--------------|

1639

DATE MAILED: 08/25/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.
09/780,600

Applicant(s)
Lam et al

Examiner
Maurie G. Baker, Ph.D.

Art Unit
1639



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on May 6, 2003 and May 16, 2003
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 46-61, 63, and 64 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 46-60, 63, and 64 is/are rejected.
- 7) ☒ Claim(s) 61 is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5 6) ☐ Other:

DETAILED ACTION

1. The Response filed May 6, 2003 (Paper No. 8) and Supplemental Response filed May 16, 2003 (Paper No. 9) are acknowledged. Claims 62 and 65-75 were cancelled and no claims were added in Paper No. 8. Therefore, claims 46-61, 63 and 64 are pending.

Information Disclosure Statement

2. The translations of the foreign patents DD 223149 & EP 0543333 and articles by Kamel et al & Zander et al filed May 16, 2003 have been received. Thus, the information disclosure statement filed 2/09/01 has now been fully considered and a copy of the PTO-1449 is attached to this action.

Status of Objections & Rejections

3. The previous claim objections are withdrawn in view of applicant's cancellation of claims and claim amendments. The rejections specifically directed at claims 62 and 65 have also been withdrawn in view of their cancellation. The rejection under the first paragraph of 35 U.S.C. 112 for *new matter* is withdrawn in view of applicant's amendments and arguments. Part of the other rejection under the first paragraph of 35 U.S.C. 112 and the rejections under the second paragraph of 35 U.S.C. 112 are withdrawn in view of applicant's amendments and arguments; however, parts of the previous rejections are maintained. Responses to applicant's arguments are set forth following each rejection. **Please especially note paragraph 10.**

Maintained Rejections
Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 46-60, 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds comprising *defined linkage sites on the D moiety* and a *structurally defined linkage (L)*, does not reasonably provide enablement for compounds containing **any** linkage group linked at any site of D. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is clear from applicant's specification how one might practice this invention with *defined linkage sites on the D moiety* and *defined linkers*; however, there is insufficient guidance as to how to make/use compounds comprising **any** linkage group linked at any site of D. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;

- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The breadth of the claims and the nature of the invention: The claims are drawn to compounds comprising NUC, L and D portions that are linked together. In claims 46-58, 62, 63 and 65 no limitations on the identity of L are given (defined only as "a linkage") and, as such, this could read on a wide variety of structures. Such represents very broad scope. It is noted that claims 59-61 and 64 appear to recite specific L groups and/or linkage sites on D. However, the linkage sites and the structure of the linker for these compounds is not set forth clearly (see rejections under 35 USC 112, second paragraph below), and for none of the claims are *both* defined. This also represents broad scope. The state of the prior art and the level of predictability in the art: Labeled nucleic acid compounds were known in the art at the time of filing; however, only limited numbers of such compounds were known and the specification gives no guidance to permit one of skill in the art to devise strategies for synthesis of *any* nucleic acid compound that has a dye linked thereto in any manner with any linkage group. The structures of possible variants are sufficiently diverse and one of ordinary skill would not be able to predict their structures. The limitation that the NUC, L and D portions are linked together adds to the unpredictability because the portions have various structures each of which would require completely different linkage strategies. One of ordinary skill could not guess, *a priori*, how to make and use **any** such compounds as one could

not necessarily predict the linkage site and linkage structure in the absence of any guidance without undue experimentation. Applicant's claimed scope of compounds represents only an invitation to experiment regarding possible compounds with undefined linkage sites linked with linkers of undefined structure. The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. Such persons of ordinary skill in this art, given its unpredictability, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed. The amount of direction provided by the inventor and the existence of working examples: Applicants have only provided very limited examples of compounds within the scope of the claims. These examples only show the NUC and D portions linked together in a *defined* manner, with a *defined* L group. No generic strategy for determining linkage sites on the D moiety is provided. The teachings of the instant specification coupled with the examples only supports specific labeled nucleic acid compounds that are linked at a *defined linkage site of D* with a *defined linkage group (L)*. The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in making and using the full scope of the claimed compounds. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496

& n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Response to Arguments

6. Applicant's arguments filed May 6, 2003 have been carefully considered but are not found fully persuasive. The examiner's rationale is set forth below.

7. It is first noted that applicant argues that the examiner's reasoning is in conflict with the rejection. The rejection was set forth on the grounds that only compounds comprising *defined linkage sites on the D moiety* and a *structurally defined linkage (L)* were enabled. A structurally defined linkage (L) would be one that is specifically set forth by structure and a defined linkage site on the D moiety would be a specific site denoted on the dye where attachment occurs. As stated in the rejection, for none of the claims are *both* defined (although it was noted that for some of the claims one or the other was defined). However, after careful consideration of the Response and reconsideration of the instant specification, applicant's arguments are found persuasive with respect to the enablement of the claims for any linkage.

8. However, the portion of the rejection based on the *defined linkage sites on the D moiety* is maintained. The examiner's position is that the claimed scope of compounds represents only an invitation to experiment regarding possible compounds with undefined linkage sites on the D moiety. One of ordinary skill could not necessarily predict the linkage site in the absence of any guidance without undue experimentation, as such would be unpredictable. It is noted that claim 61, which does define the linkage site of L to D, is deemed to be enabled. See also paragraph 10 below.

9. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. See *In re Fisher*, 57 CCPA 1099, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Additionally, the Board has held on the issue of unpredictability that "... the unpredictability of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." *Ex parte Singh*, 17 U.S.P.Q.2d 1714, 1716 (B.P.A.I. 1990).

10. For the reasons set forth above, the rejection under 35 U.S.C. 112, first paragraph is maintained. However, the instant specification sets forth preferred positions for the linkage site on the D moiety on page 57, line 17. Limitation of the claims to these linkage sites for the attachment of L to D would obviate the above rejection.

***Maintained Rejections
Claim Rejections - 35 USC § 112***

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 50 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- A. Withdrawn.
- B. Withdrawn.
- C. Amended claims 50 and 53 include in the definitions of R₈ a “linking group”. These claims remain confusing and indefinite, as it is unclear if the “linking group” is the same or different from the L set forth in independent claim 46.
- D. Withdrawn.
- E. Withdrawn.
- F. Withdrawn.

Response to Arguments

13. Applicant's arguments filed May 6, 2003 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

14. Applicant states that the amendments to claims 50 and 53 obviates the rejection. The examiner respectfully disagrees, as it is still unclear whether "linking group" is the same or different from the L set forth in independent claim 46. It appears that perhaps this "linking group" links the Dye (D) to L (as defined in claim 46). If so, this should be clearly set forth in the claims.

Status of Claims/Conclusion

15. Claim 61 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the

date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

18. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.
August 22, 2003



MAURIE GARCIA BAKER PH.D.
PRIMARY EXAMINER